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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(54) Title: NOVEL FORMULATIONS COMPRISING LIPID-REGULATING AGENTS

## (57) Abstract

The present invention is directed to a formulation comprising a lipid-regulating agent dissolved in at least one propylene glycol fatty acid ester as the primary solvent medium for said agent. One or more emulsifiers may be added to the formulation.

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Novel Formulations Comprising  
Lipid-Regulating Agents

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Field of the Invention

The present invention relates to novel formulations for oral administration comprising lipid-regulating agents.

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Background of the Invention

2-[4-(4-chlorobenzoyl)phenoxy]-2-methyl-propanoic acid, 1-methylethylester, also known as fenofibrate, is representative of a broad class of compounds having pharmaceutical utility as lipid regulating agents. More specifically, this compound is part of a lipid-regulating agent class of compounds commonly known as fibrates, and is disclosed in U.S. Patent No. 4,058,552.

20 Fenofibrate has been prepared in several different formulations, c.f., U.S. Patent No. 4,800,079 and U.S. Patent No. 4,895,726. U.S. Patent No. 4,895,726 discloses a co-micronized formulation of fenofibrate and a solid surfactant.

25 U.S. Patent No. 4,961,890 discloses a process for preparing a controlled release formulation containing fenofibrate in an intermediate layer in the form of crystalline microparticles included within pores of an inert matrix. The formulation is prepared by a process involving the sequential steps of dampening said inert core with a solution based on said binder, then projecting said fenofibrate microparticles in a single layer onto said dampened core, and thereafter drying, before said solution based on said binder dissolves said fenofibrate microparticles, and repeating said three steps in sequence until said 30 intermediate layer is formed.

35 European Patent Application No. EP0793958A2 discloses a process for producing a fenofibrate solid dosage form utilizing fenofibrate, a surface active agent and polyvinyl pyrrolidone in which the fenofibrate particles are mixed with a polyvinyl pyrrolidone solution. The thus obtained mixture is granulated with an aqueous solution of one or more surface active agents, and the granulate thus produced is dried.

PCT Publication No. WO 82/01649 discloses a fenofibrate formulation having granules that are comprised of a neutral core that is a mixture of saccharose and starch. The neutral core is covered with a first layer of fenofibrate, admixed with an excipient and with a second microporous outer layer of an edible polymer.

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U.S. Patent No. 5,645,856 describes the use of a carrier for hydrophobic drugs, including fenofibrate, and pharmaceutical compositions based thereon. The carrier comprises a digestible oil and a pharmaceutically-acceptable surfactant component for dispersing the oil in vivo upon administration of the carrier, which comprises a hydrophilic 10 surfactant, said surfactant component being such as not to substantially inhibit the in vivo lipolysis of the digestible oil.

10

Gemfibrozil is another member of the fibrate class of lipid-regulating agents. U.S. Patent No. 4,927,639 discloses a disintegratable formulation of gemfibrozil providing both 15 immediate and sustained release, comprising a tablet compressed from a mixture of a first and second granulation, and a disintegration excipient operable to effect partial or complete disintegration in the stomach. The first granulation comprises finely divided particles of pure gemfibrozil granulated with at least one cellulose derivative, and the second granulation comprises finely divided particles of pure gemfibrozil granulated with a 20 pharmaceutically-acceptable water soluble or insoluble polymer which are then uniformly coated with a pharmaceutically-acceptable (meth)acrylate copolymer prior to admixture with the first granulation. The first and second granulations are present in the final composition in a ratio of from about 10:1 to about 1:10.

20

U.S. Patent 4,925,676 discloses a disintegratable gemfibrozil tablet providing both 25 immediate and enteric release, which is compressed from a mixture of a first granulation of gemfibrozil with at least one acid-disintegratable binder, and a second granulation formed from the first granulation, but regranulated or coated with an alkali-disintegratable formulation of at least one substantially alkali-soluble and substantially acid-insoluble 30 polymer.

Another class of lipid-regulating agents are commonly known as statins, of which pravastatin and atorvastatin are members. U.S. Patents 5,030,447 and 5,180,589 describe 35 stable pharmaceutical compositions, which when dispersed in water have a pH of at least 9, and include a medicament which is sensitive to a low pH environment, such as pravastatin, one or more fillers such as lactose and/or microcrystalline cellulose, one or more binders, such as microcrystalline cellulose (dry binder) or polyvinylpyrrolidone (wet binder), one or

more disintegrating agents such as croscarmellose sodium, one or more lubricants such as magnesium stearate and one or more basifying agents such as magnesium oxide.

5 It is an object of the present invention to provide formulations for oral administration comprising lipid-regulating agents having enhanced bioavailability when compared to commercially available formulations.

#### Summary of the Invention

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The present invention is directed to formulations for oral administration comprising a lipid-regulating agent, further comprising at least one propylene glycol fatty acid ester as the primary solvent medium for the lipid-regulating agent. One or more emulsifiers may optionally be added to the formulation.

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The formulation may be administered directly, diluted into an appropriate vehicle for administration, encapsulated into soft or hard gelatin shells or capsules for administration, or administered by other means obvious to those skilled in the art.

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#### Brief Description of the Drawings

Figure 1 is a graph showing the plasma concentration in fasted dogs of the formulation of Example 1 and a reference composition.

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Figure 2 is a graph showing the plasma concentration in fasted dogs of the formulation of Example 2 and a reference composition.

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Figure 3 is a graph showing the plasma concentration in fasted and non-fasted dogs of the formulation of Example 1 and a reference composition.

#### Detailed Description of the Invention

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The bulk lipid-regulating agent can be prepared by any available method, as for example the compound fenofibrate may be prepared by the procedure disclosed in U.S.

Patent No. 4,058,552 or the procedure disclosed in U.S. Patent No. 4,739,101, both herein incorporated by reference.

5 Representative propylene glycol fatty acid esters include, but are not limited to, propylene glycol dicaprylate/dicaprate, propylene glycol dicaprate, propylene glycol laurate, and propylene glycol mono- and dicaprylate.

10 Preferred propylene glycol fatty acid esters include Miglyol 840<sup>TM</sup>, a propylene glycol dicaprylate/dicaprate available from Creanova; Captex 100<sup>TM</sup>, a propylene glycol dicaprate available from Abitec; Lauroglycol<sup>TM</sup>, a propylene glycol laurate available from 15 Gattefosse; and Capmul PG8<sup>TM</sup>, a propylene glycol mono- and dicaprylate available from Abitec.

15 Suitable emulsifiers include pharmaceutically-acceptable emulsifiers such as, for example, TPGS (d-alpha tocopheryl polyethylene glycol 1000 succinate), phospholipids, polyoxyethylene sorbitan fatty acid derivatives, castor oil or hydrogenated castor oil ethoxylates, polyglycerol esters of fatty acids, fatty acid ethoxylates, alcohol ethoxylates, and polyoxyethylene-polyoxypropylene co-polymers and block co-polymers. Preferred emulsifiers include castor oil or hydrogenated castor oil ethoxylates. A more preferred 20 emulsifier is Cremophor EL<sup>TM</sup>, a polyoxyl 35 castor oil, available from BASF.

25 Other optional ingredients which may be included in the compositions of the present invention are those which are conventionally used in oil-based drug delivery systems, e.g. antioxidants such as, for example, tocopherol, ascorbyl palmitate, ascorbic acid, butylated hydroxytoluene, butylated hydroxyanisole, propyl gallate, etc.; pH stabilizers such as, for example, citric acid, tartaric acid, fumaric acid, acetic acid, glycine, arginine, lysine, potassium hydrogen phosphate, etc.; thickeners/suspending agents such as, for example, 30 hydrogenated vegetable oils, beeswax, colloidal silicon dioxide, gums, celluloses, silicates, bentonite, etc.; flavoring agents such as, for example, cherry, lemon, aniseed flavors, etc.; sweeteners such as, for example, aspartame, saccharin, cyclamates, etc.; and co-solvents, such as, for example, ethanol, propylene glycol, dimethyl isosorbide, etc.

35 The solution comprising the lipid-regulating agent is prepared by dissolving said agent in the propylene glycol fatty acid ester with adequate mixing at or about room temperature. If an emulsifier is used, it is added to the propylene glycol fatty acid ester with mixing prior to addition of said agent.

The resulting premix liquid comprising said agent may be dosed directly for oral administration, diluted into an appropriate vehicle for oral administration, filled into soft or hard gelatin capsules for oral administration, or delivered by some other means obvious to those skilled in the art. The said premix liquid can be used to improve the oral  
5 bioavailability, and/or increase the solubility of said agent.

The invention will be understood more clearly from the following non-limiting representative examples.

10

Example 1

Capmul PG8 (Abitec) (8.3 gm) was added to a scintillation vial. Cremophor EL (BASF) (1.0 gm) was added to the vial and mixed until uniform. Fenofibrate (Sigma) (0.7 gm) was then added to the vial and mixed until it was completely dissolved. 957 mg. of the premix (containing 67 mg. fenofibrate) was added to each of six soft gelatin capsules using  
15 a syringe. The capsules were heat-sealed and stored.

Example 2

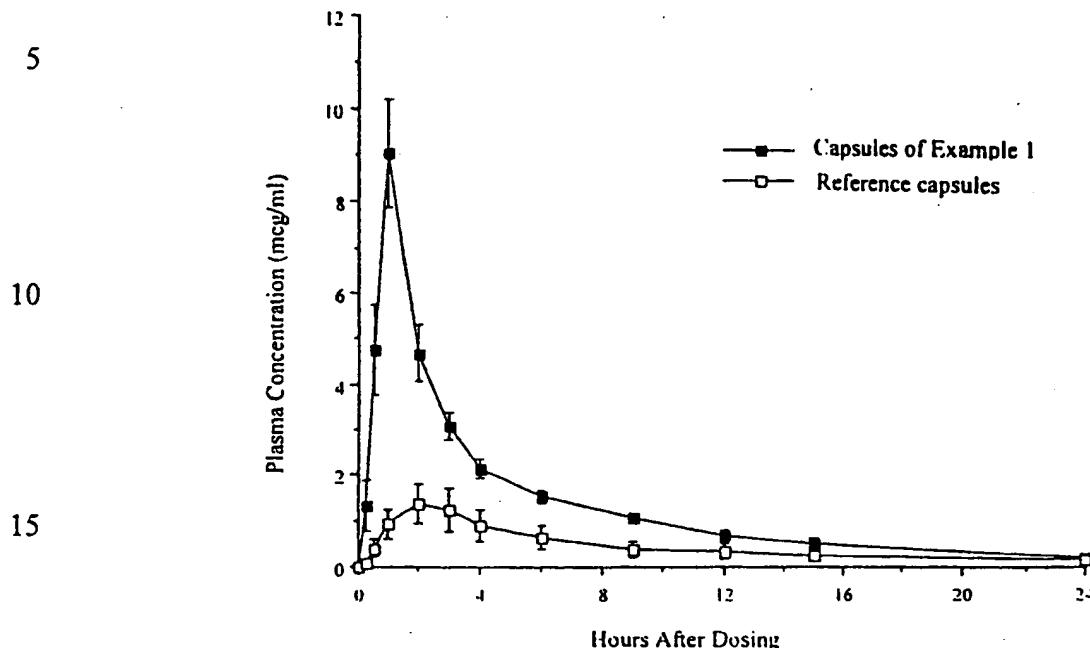
Captex 200 (propylene glycol dicaprylate/dicaprate) (Abitec)(9.3 gm) was added to a scintillation vial. Fenofibrate (Sigma) (0.7 gm) was added to the Captex 200 and mixed  
20 until completely dissolved. 957 mg. of the premix (containing 67 mg. fenofibrate) was added to each of six soft gelatin capsules using a syringe. The capsules were heat-sealed and stored.

Example 3

25 Capsules prepared by the process described in Example 1 and 2, and from a commercial fenofibrate composition, Lipanthyl 67M (Groupe Fournier) (reference), were administered to a group of dogs at a dose of 67 mg/dog (one capsule per dog). The plasma concentrations of fenofibric acid were determined by HPLC. Concentrations were normalized to a 6.7 mg/kg dose in each dog. Figures 1-3 present the resulting data in graph  
30 form.

Figure 1

Mean ( $\pm$ SEM, n=6) Plasma Concentrations of Fenofibric Acid after a 67 mg Capsule Dose of Fenofibrate in Fasted Dogs



Note: 67 mg dose administered to n=6 dogs; concentrations normalized to a 6.7 mg/kg dose.

The results, provided as mean  $\pm$  SD, n = 6 were as follows:

Lipanthyl 67M (Reference):

C<sub>max</sub> = 1.88  $\pm$  0.97 mcg/ml

T<sub>max</sub> = 1.6  $\pm$  0.9 hr

t<sub>1/2</sub> = 4.5 hr

AUC (0-24) = 11.08  $\pm$  9.42 mcg $\cdot$ hr/ml

F(%) = 21.1  $\pm$  11.8

Capsules of Example 1:

C<sub>max</sub> = 9.21  $\pm$  2.61 mcg/ml

T<sub>max</sub> = 0.9  $\pm$  0.2 hr

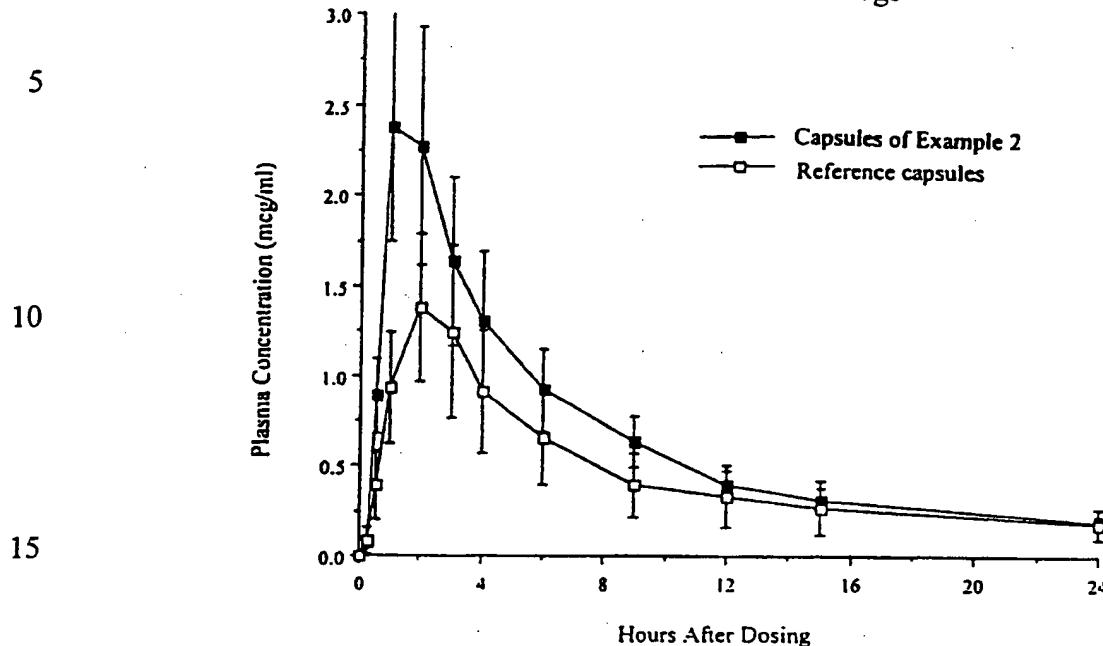
t<sub>1/2</sub> = 4.5 hr

AUC (0-24) = 33.22  $\pm$  5.81 mcg $\cdot$ hr/ml

F(%) = 70.4  $\pm$  13.2

Figure 2

Mean ( $\pm$ SEM, n=6) Plasma Concentrations of Fenofibric Acid after a 67 mg Capsule Dose of Fenofibrate in Fasted Dogs



Note: 67 mg dose administered to n=6 dogs; concentrations normalized to a 6.7 mg/kg dose.

20

The results, provided as mean  $\pm$  SD, n = 6 were as follows:

Lipanthyl 67M (Reference):

C<sub>max</sub> = 1.88  $\pm$  0.97 mcg/ml

25

T<sub>max</sub> = 1.6  $\pm$  0.9 hr

t<sub>1/2</sub> = 4.5 hr

AUC (0-24) = 11.08  $\pm$  9.42 mcg•hr/ml

F(%) = 21.1  $\pm$  11.8

30

Capsules of Example 2:

C<sub>max</sub> = 2.67  $\pm$  1.67 mcg/ml

T<sub>max</sub> = 1.3  $\pm$  0.5 hr

t<sub>1/2</sub> = 8.1 hr

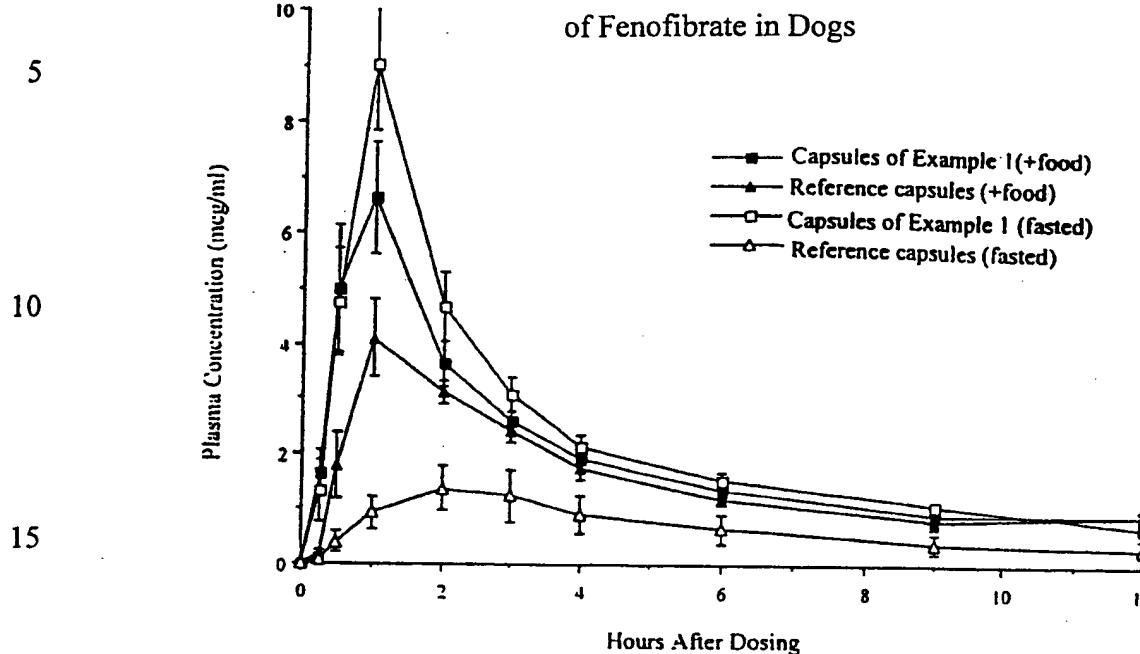
AUC (0-24) = 16.14  $\pm$  8.99 mcg•hr/ml

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F(%) = 32.8  $\pm$  15.0

Figure 3

Effect of Food on the Mean ( $\pm$ SEM, n=6) Plasma Concentrations  
of Fenofibric Acid after a 67 mg Capsule Dose  
of Fenofibrate in Dogs



Note: 67 mg dose administered to n=6 dogs; concentrations normalized to a 6.7 mg/kg dose.

20

The results, provided as mean  $\pm$  SD, n = 6 were as follows:

Lipanthy 67M (Reference) (Fasted):

Cmax =  $1.88 \pm 0.97$  mcg/ml

Tmax =  $1.6 \pm 0.9$  hr

AUC (0-24) =  $11.08 \pm 9.42$  mcg $\cdot$ hr/ml

F(%) =  $21.1 \pm 11.8$

Lipanthy 67M (Reference) (Non-fasted):

Cmax =  $4.47 \pm 1.37$  mcg/ml

Tmax =  $1.3 \pm 0.5$  hr

AUC (0-24) =  $25.44 \pm 4.28$  mcg $\cdot$ hr/ml

F(%) =  $54.8 \pm$

35 Capsules of Example 1 (Fasted):

Cmax =  $9.21 \pm 2.61$  mcg/ml

Tmax =  $0.9 \pm 0.2$  hr

AUC (0-24) =  $33.22 \pm 5.81$  mcg•hr/ml

F(%) =  $70.4 \pm 13.2$

Capsules of Example 1 (Non-fasted):

5 Cmax =  $6.79 \pm 2.59$  mcg/ml

Tmax =  $0.8 \pm 0.3$  hr

AUC (0-24) =  $31.88 \pm 8.25$  mcg•hr/ml

F(%) =  $68.3 \pm$

Example 4

5 Capmul PG8 (Abitec) (8.0 gm) is added to a scintillation vial. Cremophor EL (BASF) (1.0 gm) is added to the vial and mixed until uniform. Pravastatin (Pravachol<sup>TM</sup>, Bristol Myers Squibb) (1.0 gm) is then added to the vial and mixed until uniformly dispersed. The premix may be added to soft gelatin capsules in an amount sufficient to deliver the desired dose.

Example 5

10 Capmul PG8 (Abitec) (8.0 gm) is added to a scintillation vial. Cremophor EL (BASF) (1.0 gm) is added to the vial and mixed until uniform. Atorvastatin (Lipitor<sup>TM</sup>, Parke-Davis/Pfizer) (1.0 gm) is then added to the vial and mixed until uniformly dispersed. The premix may be added to soft gelatin capsules in an amount sufficient to deliver the desired dose.

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Claims

1. A composition comprising a lipid-regulating agent dissolved in at least one propylene glycol fatty acid ester.

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2. A composition of claim 1 wherein the lipid-regulating agent is a fibrate.

3. A composition of claim 2 wherein the fibrate is fenofibrate.

10

4. A composition of claim 1 wherein the lipid-regulating agent is a statin.

5. A composition of claim 4 wherein the statin is pravastatin or atorvastatin

6. A composition of claim 1 wherein at least one or more of the propylene glycol fatty acid esters is selected from propylene glycol dicaprylate/dicaprante, propylene glycol dicaprate, propylene glycol laurate, and propylene glycol mono- and dicaprylate.

7. A composition of claim 6 wherein at least one or more of the propylene glycol fatty acid esters is selected from a propylene glycol dicaprate and a propylene glycol mono- and dicaprylate.

20 8. A composition of claim 7 wherein at least one propylene glycol fatty acid ester is a propylene glycol mono- and dicaprylate.

25 9. A composition of claim 1 further comprising at least one emulsifier.

10. A composition of claim 9 wherein at least one emulsifier is selected from castor oil or hydrogenated castor oil ethoxylates.

30 11. A composition of claim 10 wherein the castor oil or hydrogenated castor oil ethoxylates is a polyoxyl 35 castor oil.

12. A composition of claim 1 that contains a therapeutically-effective amount of a lipid-regulating agent.

35 13. A composition of claim 12 wherein the lipid-regulating agent is a fibrate.

14. A composition of claim 13 wherein the fibrate is fenofibrate.
15. A composition of claim 12 wherein the lipid-regulating agent is a statin.
- 5 16. A composition of claim 15 wherein the statin is pravastatin or atorvastatin.
17. A capsule comprising a composition of claim 1.
18. A capsule of claim 17 wherein the lipid-regulating agent is a fibrate.
- 10 19. A capsule of claim 18 wherein the fibrate is fenofibrate.
20. A capsule of claim 17 wherein the lipid-regulating agent is a statin.
- 15 21. A capsule of claim 20 wherein the statin is pravastatin or atorvastatin.
22. A method of treating hyperlipidemia comprising the administration of a composition of claim 1 to a patient.

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- 20 23. A method of treating hyperlipidemia comprising the administration of a composition of claim 12 to a patient.
24. A method of claim 23 wherein the lipid-regulating agent is a fibrate.
- 25 25. A method of claim 24 wherein the fibrate is fenofibrate.
26. A method of claim 23 wherein the lipid-regulating agent is a statin.
27. A method of claim 26 wherein the statin is pravastatin or atorvastatin
- 30 28. A composition of claim 1 further comprising at least one co-solvent.
29. A composition of claim 28 wherein at least one co-solvent is selected from ethanol, propylene glycol, and dimethyl isosorbide.
- 35 30. A method of claim 22 wherein the patient may be a fasted or non-fasted patient.

31. A method of claim 30 wherein the patient is a fasted patient.
32. A method of claim 30 wherein the patient is a non-fasted patient.

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| <b>(51) International Patent Classification 7 :</b><br><b>A61K 9/48, 47/14, A61P 3/04</b>   |  | <b>A3</b>  | <b>(11) International Publication Number:</b> <b>WO 00/37057</b><br><b>(43) International Publication Date:</b> <b>29 June 2000 (29.06.00)</b> |
| <b>(21) International Application Number:</b> <b>PCT/US99/29696</b><br><b>(22) International Filing Date:</b> <b>15 December 1999 (15.12.99)</b>  |  | <b>(81) Designated States:</b> CA, JP, MX, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).<br><br><b>Published</b><br><i>With international search report.</i> |  |
| <b>(30) Priority Data:</b><br>09/216,448 18 December 1998 (18.12.98) US   |  | <b>(88) Date of publication of the international search report:</b> <b>16 November 2000 (16.11.00)</b>   |  |
| <b>(71) Applicant:</b> ABBOTT LABORATORIES [US/US];<br>CHAD-0377/AP6D-2, 100 Abbott Park Road, Abbott Park, IL 60064-6050 (US).<br><br><b>(72) Inventors:</b> LIPARI, John, M.; 6600 Apollo Drive, Racine, WI 53406 (US). RAYMOND, Dawn, M.; 274 Barbara Avenue, Solana Beach, CA 92075 (US). REILAND, Tom; 33974 N. Lake Short Drive, Gages Lake, IL 60030 (US).<br><br><b>(74) Agents:</b> SICKERT, Dugal, S. et al.; Abbott Laboratories, CHAD 0377/AP6D-2, 100 Abbott Park Road, Abbott Park, IL 60064-6050 (US). |  |  |  |
| <b>(54) Title:</b> NOVEL FORMULATIONS COMPRISING LIPID-REGULATING AGENTS  |  |  |  |
| <b>(57) Abstract</b><br><br>The present invention is directed to a formulation comprising a lipid-regulating agent dissolved in at least one propylene glycol fatty acid ester as the primary solvent medium for said agent. One or more emulsifiers may be added to the formulation.   |  |  |  |

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# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 99/29696

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 7 A61K9/48 A61K47/14 A61P3/04

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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| Category * | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No.               |
|------------|--|-------------------------------------|
| X          | <p>WO 92 10996 A (MERRELL DOW PHARMA)<br/>9 July 1992 (1992-07-09)</p> <p>page 1, line 5 - line 8<br/>page 2, line 1 - line 12<br/>page 3, line 14 - line 26<br/>page 4, line 21 - line 28<br/>page 6, line 35 -page 7, line 5; table II<br/>claims; example 1</p> <p>-----</p> <p style="text-align: center;">-/-</p> | 1,6,7,<br>12,17,<br>22,23,<br>28-30 |
|            |  |                                     |

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

\* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
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Date of the actual completion of the international search

7 August 2000

Date of mailing of the international search report

18/08/2000

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Marttin, E

## INTERNATIONAL SEARCH REPORT

|                              |
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| International Application No |
| PCT/US 99/29696              |

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No.                |
|------------|---|--------------------------------------|
| X          | <p>DATABASE CHEMABS 'Online!<br/>CHEMICAL ABSTRACTS SERVICE, COLUMBUS,<br/>OHIO, US;</p> <p>KOUJI, MINORU ET AL: "Composition of<br/>pharmaceutical preparation improved in<br/>peroral absorbability"<br/>retrieved from STN<br/>Database accession no. 123:152928<br/>XP002144199<br/>abstract<br/>&amp; WO 95 14463 A (TAISHO PHARMACEUTICAL<br/>CO., LTD., JAPAN) 1 June 1995 (1995-06-01)<br/>--</p>   | 1,6,9,<br>12,17,<br>22,23            |
| A          | <p>US 5 645 856 A (LACY JONATHAN ERNEST ET<br/>AL) 8 July 1997 (1997-07-08)<br/>cited in the application</p> <p>column 1, line 4 - line 7<br/>column 3, line 56 -column 4, line 14<br/>column 4, line 36 -column 5, line 51<br/>column 6, line 34 -column 7, line 55<br/>column 8, line 45 -column 9, line 14<br/>column 12, line 22 - line 23<br/>column 12, line 54 -column 13, line 7<br/>column 13, line 47 - line 57; claims<br/>1-8,15-17; example 7<br/>--</p> | 1-3,<br>6-14,<br>17-19,<br>22-25,30  |
| E          | <p>EP 0 998 927 A (FUJIREBIO KK)<br/>10 May 2000 (2000-05-10)</p> <p>page 2, paragraph 2 - paragraph 4<br/>page 2, last paragraph -page 3, paragraph<br/>1<br/>page 3, paragraph 10 - paragraph 13<br/>claims; examples 2,3,10-12,14<br/>----</p>   | 1,6-10,<br>12,17,<br>22,23,<br>30-32 |

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-32 relate to a compound defined by reference to a desirable characteristic or property, namely a "lipid-regulating agent". The term "lipid-regulating agent" as used in the present independent claims 1, 17, 22 and 23 in dependent claims 2-16, 18-21, and 24-32 defines the active agent by its pharmacological effect. However, a compound cannot be sufficiently characterised by its pharmacological effect as it is done by an expression like "lipid-regulating agent", because it is impossible to know which substances are encompassed in this expression. Moreover, a compound cannot be sufficiently characterised by the term "regulating", because this term has no well-recognised meaning and is therefore unclear.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for the concept of "lipid-regulating agent" and those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds mentioned in claims 2-5.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/29696

| Patent document cited in search report | Publication date | Patent family member(s) |   | Publication date |
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